Chiral organometallic reagents. Part XXIV.[1] Iodine ate-complexes as intermediates in the iodine–lithium exchange reaction on 1,1-diiodoalkanes

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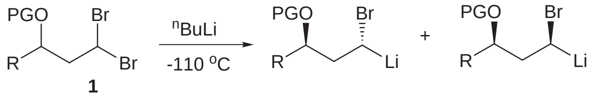
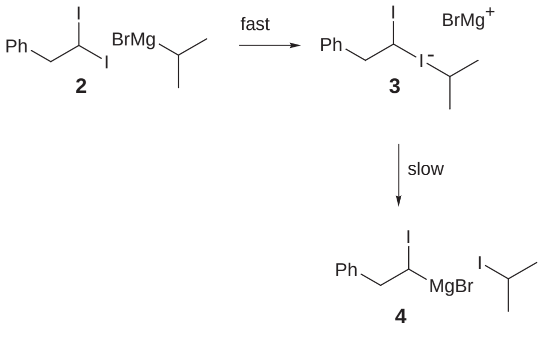
The iodine–lithium exchange reaction on the 1,1-diiodoalkanes **17** at −110 °C is initiated by the irreversible formation of yellow iodine ate-complexes, which are slowly transformed into the α-iodoalkyllithium compounds **21**.

Introduction

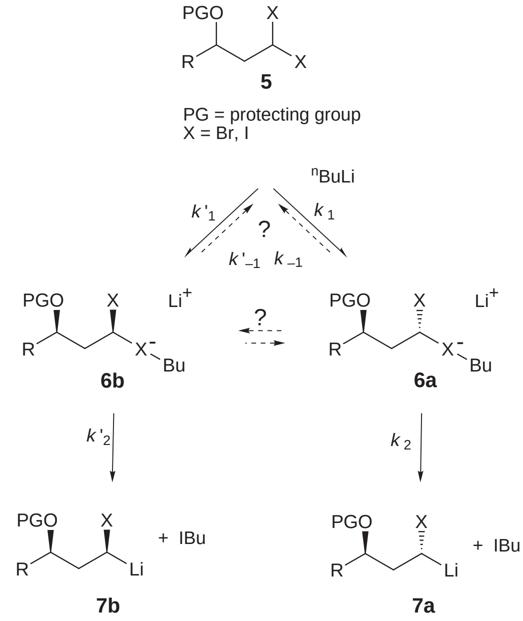
We have previously reported on the differentiation of diastereotopic bromine atoms in a bromine–lithium exchange reaction on various β- and γ-substituted 1,1-dibromoalkanes **1**.[2,3] We have put forward some ideas about how a conformational preorganization of the substrate dibromoalkanes affects the sense of the asymmetric induction.[4]



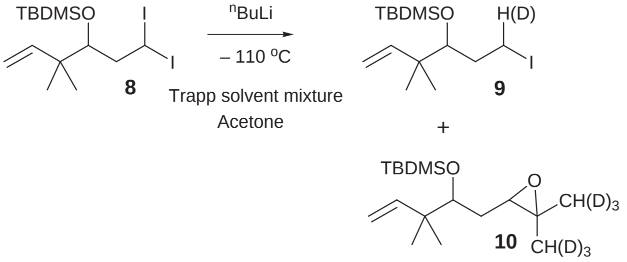
Any discussion of the nature of the stereodifferentiating step has to address the mechanism of the bromine–lithium exchange reaction, which had been postulated by Wittig[5] to proceed *via* halogen ate-complexes. The indirect kinetic evidence,[6] followed by spectroscopic observations[7] and finally a crystal structure determination[8] lend credence to the notion that such ate-complexes are true intermediates and not merely high energy constellations or transition states in the halogen–metal exchange reaction. Recently the stoichiometric formation of long-lived iodine ate-complexes **3** was demonstrated in the iodine–magnesium exchange reaction on 1,1-diiodoalkanes **2**.[9]



We therefore readdressed the question of the stereodefining step in the halogen–lithium exchange reactions on compounds of the type **1**. When ate-complexes **6** are intermediates in the halogen–metal exchange reaction, the stereoselectivity on reaction of the diiodoalkane **5** to give the lithium compound **7** may be defined either in the formation or in the subsequent transformation of the ate-complexes **6** to give **7**. This depends on whether the formation of **6** is irreversible or reversible. The latter would constitute a Curtin–Hammett situation.



This investigation was stimulated by the observation that significant amounts of protonation products **9** are formed on reaction of the 1,1-diiodoalkane **8** with butyllithium in the presence of acetone.[10] We surmised (but could not in the end substantiate, see below) that **9** could arise by protonation of long-lived ate-complex intermediates **12**. In fact, a reaction of **8** in the presence of deuteroacetone proved that acetone is the proton source, since monodeuterated **9** was formed.



CH_3COCH_3 **9** + **10** = 90% **9**:**10** = 73 : 23
CD_3COCD_3 **9-d$_1$** + **10-d$_6$** = 86% **9-d$_1$**:**10-d$_6$** = 63 : 37

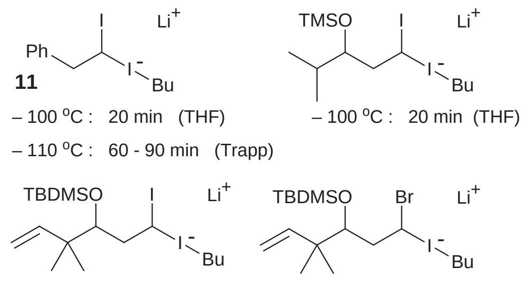
The product ratios obtained on quenching with acetone or deuteroacetone respectively revealed a partitioning isotope effect, but it remained unknown whether partitioning occurred at the stage of the ate-complexes **6** or the lithium compounds **7**.

Experience with the ate-complexes **3** with magnesium as counter ion indicated[9] that α-iodoalkyl iodine ate-complexes should be the most stable ones and also the longest lived of all α-halogenoalkyl halogen ate-complexes.[11] This led us to scrutinize more closely the iodine–lithium exchange reaction of 1,1-diiodoalkanes hoping to define the role of α-iodoalkyl iodine ate-complexes in these processes.

Qualitative evidence for α-iodoalkyl iodine ate-complexes

The α-iodoalkyl iodine ate-complex **3** with a magnesium counter ion has a strong absorption in the visible ($\lambda_{max} = 409$ nm, $\varepsilon \approx 500$ L mol^{-1} cm^{-1}) forming intensely pumpkin-yellow solutions.[9] The formation and decay of such ate-complexes are easily monitored by following the color change. Indeed, when the 1,1-diiodoalkane **2** was treated at −100 °C in a Trapp solvent mixture[12] with *n*-butyllithium the solution acquired a deep yellow color, indicative of the formation of **11**, which faded after 20 min.[13] Likewise, reaction of **8** with *n*-butyllithium in a Trapp solvent mixture led to an intensive yellow coloration which persisted for up to 60 min. Some further observations are given below.

Persistence of the Yellow Color
(Trapp = Trapp solvent mixture)



11

– 100 °C : 20 min (THF)

– 110 °C : 60 - 90 min (Trapp)

– 100 °C : 20 min (THF)

12

– 110 °C : 60 min (Trapp)

13

– 110 °C : 5 min (Trapp)

Even with an α-bromoiodo-compound the color characteristic for the ate-complexes **13** could be seen, although it faded much more rapidly. Thus, by *prima facie* evidence the color of the solution suggests the formation of long-lived ate-complexes also in the iodine–lithium exchange reaction on 1,1-diiodoalkanes at low temperatures.

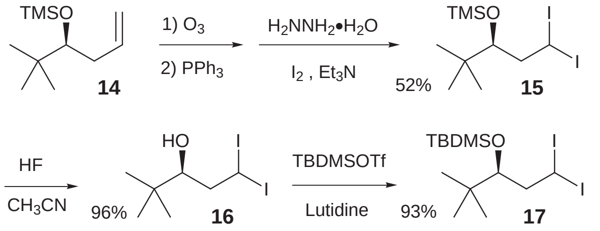
The ate-complexes **3** and the Grignard reagent **4** have been differentiated by an isotope effect on quenching into a 1 : 1 mixture of CH_3OD and CH_3OH.[9] Thus, quenching of the yellow solution into CH_3OD–CH_3OH, 5 to 30 min after interaction of the diiodo-compound **2** with butyllithium at −110 °C, occured with an apparent isotope effect of k_H/k_D of 0.6. Quenching of the solution after 2.5 hours, when the yellow color of the solution had faded, proceeded with an apparent isotope effect of k_H/k_D of 1.1. This shows that at least two different species, which can be protonated, are present in the solution in substantial amounts, when the solution is colored and when it has become colorless. We therefore reason that the yellow ate-complexes **11** are initially formed in a stoichiometric manner on reaction of the diiodoalkane **2** with butyllithium in a Trapp solvent mixture at −110 °C.

Is the formation of the ate-complexes reversible?

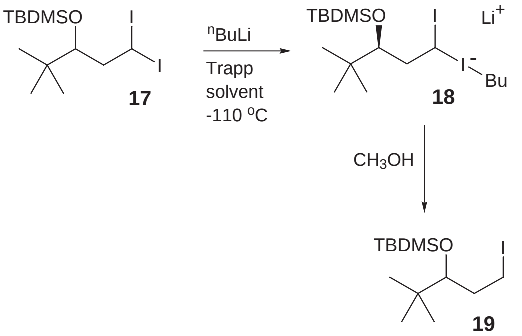
The rapid appearance and slow bleaching of the yellow color on reaction of **5** with butyllithium suggests that the ate-complexes **6** are rapidly formed and slowly transformed into the α-iodoalkyllithium compounds **7**. If the formation of the ate-complexes were reversible, *i.e.* $k_{-1} > k_2$, a Curtin–Hammett situation would prevail, in which the diastereomer ratio of the lithium compounds **7a** and **7b** is determined by the kinetic diastereomer resolution of the equilibrating ate-complexes **6a** and **6b**. In this case the product ratio derived from **7** could be different from the ratio of the ate-complexes **6**.

On the other hand, if the formation of the ate-complexes **6** was irreversible, the ratio of the lithium compounds **7** and the product ratio derived thereof should reflect the ratio of the ate-complexes **6**. The ate-complexes **6** appear to be instantaneously quenched by addition of methanol. This allows for the determination of the ratio of the ate-complexes **6** by quenching with CH_3OD either *in situ* or within the first minutes after the formation of the ate-complexes, when the solution is still intensely yellow colored. The ratio of the α-iodoalkyllithium compounds **7** in turn can be derived from quenching of the decolorized solutions after the appropriate period of time.

These aspects have been studied in a series of experiments using the diiodoalkane **17**, which has been prepared from the alkene **14**[14] by ozonolysis and iodination of the hydrazone.[15] The latter reaction gave rise to several side products. Separation of the desired product became possible after conversion of the TMS ether **15** into the alcohol **16**. The latter was ultimately reprotected with TBDMS-triflate to give racemic **17**.



Treatment of the diiodoalkane **17** with *n*-butyllithium in a Trapp solvent mixture[12] at −110 °C generated the intense yellow color of the ate-complexes **18**, which persisted for *ca.* 30 min under these conditions. When a precooled solution of CH_3OH was added in a two-compartment reaction vessel[10] to such yellow solutions, the color was immediately discharged, resulting in the quantitative formation of the monoiodoalkane **19**.



Quenching of the ate-complexes **18** with CH_3OD, C_6H_5SD or CD_3COCD_3 generated the mono-deuterated compounds **20**, the diastereoisomer ratio of which was determined by ^{2}D-NMR spectroscopy. The results are compiled in Table 1.

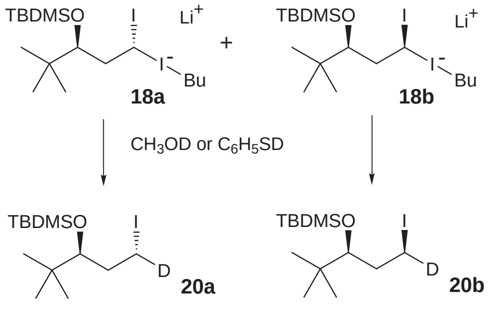
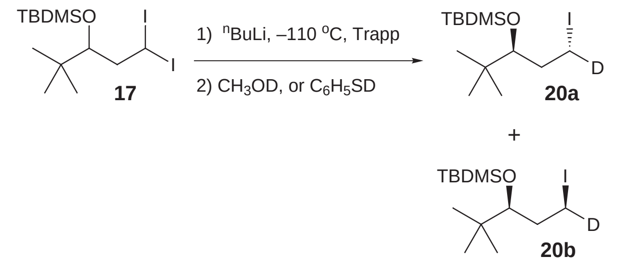


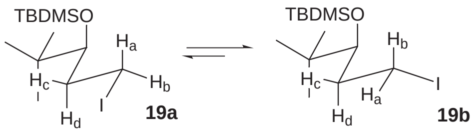
Table 1



Addition after	Yield	Ratio **20a/20b**
Quenching with CH_3OD		
in situ	80%	68:32
1 min	77%	70:30
5 min	80%	72:28
5 min[a]	65%	73:27
5 min[b]	74%	68:32
30 min	78%	70:30
Quenching with C_6H_5SD		
in situ	20%	70:30
1 min	48%	74:26
5 min	45%	74:26
30 min	43%	68:32

[a] In the presence of 2 equiv. of DMPU. [b] In the presence of 2 equiv. of HMPT.

A detailed analysis of the coupling constants in the ^{1}H-NMR spectrum of **19** allowed an assignment of the diastereotopic hydrogen atoms H_a and H_b in **19** resonating at 3.34 and 3.14 ppm. MM3* calculations[16] indicate that **19** populates mainly two conformations **19a** and **19b**. This allowed us to calculate population averaged $^3J_{H,H}$ coupling constants for **19**.



Coupling constants (Hz)

Calculated for	19a	19b	Population averaged	Experimental
H_a H_c	3.6	4.9	4.5	4.8
H_a H_d	13.1	2.4	9.1	8.7
H_b H_c	13.3	1.5	9.0	8.2
H_b H_d	2.2	13.2	5.8	8.3

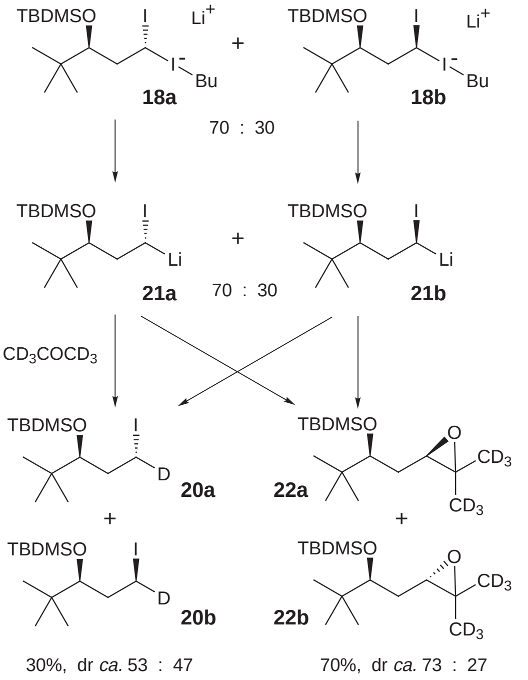
It is evident that the signal at 3.34 ppm with the small coupling constant (4.7 Hz) corresponds to H_a, whereas the signal at 3.14 ppm with the large coupling constants stems from H_b. This allowed the structure of the predominant diastereomer of the deuterated compound **20** to be assigned as **20a**.

The results obtained on quenching of the reaction mixtures with CH_3OD or C_6H_5SD show that the diastereomeric ate-complexes **18a** and **18b** are generated in a (70 ± 5):(30 ± 5) ratio. Since the same stereoisomer ratio resulted from *in situ* quenching with two equivalents of CH_3OD, it may be assumed that the ratio of the ate-complexes **18a** and **18b** is kinetically controlled. The product ratio **20a/20b** did not change upon conversion of the ate-complexes **18** into the α-iodoalkyllithium compounds **21** as seen from quenching after 5 and eventually after 30 min.

The results obtained on quenching with deuteroacetone are more complex, since in addition to the deuterated compound **20**, the epoxides **22** were formed, *cf.* Table 2. The stereostructure of the epoxides **22** has been assigned before.[2]

For all experiments in which deuteroacetone was added after the generation of the ate-complexes, the product ratio **20/22** is about 30:70, irrespective of the time of quenching. This constant partitioning ratio suggests that it is one and the same species that leads to those products. Since after 30 min the solution is colorless, *i.e.* there are no longer ate-complexes **18** present, it must be the α-iodoalkyllithium compounds **21** that are being quenched with acetone. It follows that the ate-complexes **18** do not react with acetone to give either **20** or **22** or both, a reaction that would be likely to give rise to a different ratio of **20** and **22**. Since the addition of acetone after 1 or 5 min led to a moderately rapid (*ca.* 10 min) decolorization, all that acetone possibly does is to speed up the transformation of the ate-complexes **18** into the α-iodoalkyllithium compounds **21**, which then are eventually trapped with acetone.

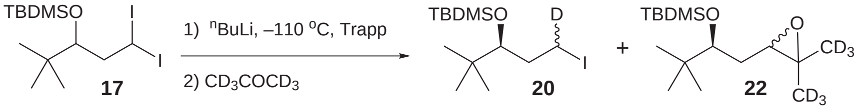
A look at the diastereomer ratios of **20** and of **22** shows them to be different from one another. These differences arise probably from a kinetic resolution in the reaction of the diastereomeric α-iodoalkyllithium compounds **21** with acetone along the two reaction pathways.



Since the individual stereostructures of the diastereomers of **20** and **22** are known, the diastereomer ratio observed for **20** and **22** can be traced back to a calculated diastereomer ratio of the organolithium compounds **21** as indicated in the last column of Table 2. The calculated values are in line with the assumption that the organolithium compounds **21a** and **21b** are generated in a *ca.* 70:30 ratio.

All the data so far are consistent with the picture that the ate-complexes **18a** and **18b** are formed in a *ca.* 70:30 ratio and that this ratio is transformed into the ratio of the lithium-compounds **21a**, **21b** with high fidelity, suggesting an irreversible formation of the ate-complexes **18a** and **18b**. There is, however, one aberrant result, which we are unable to explain at present. This is the result obtained on *in situ* trapping with deuteroacetone, *cf.* the last entry of Table 2. The yellow color of the ate complexes is observed when the diiodo-compound **17** is treated with butyllithium in the presence of two equivalents of acetone. The ratio of the deuterated products **20** to the epoxides **22** is, however, reversed compared to the results of the sequential trapping experiments. This clearly indicates that a different species other than the lithium compounds **21** is being trapped. The diastereomer ratio of the deuterated products **20a** and **20b** (67:33) and of the epoxides **22a** and **22b** (91:9) can be

Table 2



Addition of CD_3COCD_3 after	Yield (%) of **20**	Ratio **20a/20b**	Ratio **20/22**	Yield (%) of **22**	Ratio **22a/22b**	Calculated Ratio of **21a/21b**
1 min	20	53:47	29:71	50	74:26	74:26
5 min	19	54:46	31:69	34	74:26	74:26
30 min	20	56:44	27:73	45	73:27	73:27
60 min	23	52:48	27:73	58	73:27	73:27
150 min	21	54:46	30:70	56	72:28	72:28
in situ	48	67:33	63:37	27	91:9	76:24

calculated back to a diastereomer ratio of the ate-complexes **18** of 76:24, which is by and large the same as seen before (70 ± 5):(30 ± 5).

Apparently, the presence of acetone does not change the ratio in which the diastereomeric ate-complexes **18** are being formed. This is in line with the notion that polar cosolvents do not alter the ratio in which the ate-complexes **18** are being formed (*cf.* relevant entries in Table 1).

We do not have any clue as to the nature of a further intermediate between the ate-complexes **18** and the organolithium compounds **21**, an intermediate which is being trapped in these *in situ* experiments. It is puzzling that there is no gradual change between the values for the *in situ* trapping to those resulting from trapping after 1 or 5 min, at which time the ate-complexes are still present.

We have addressed in this study the role of α-iodoalkyliodine ate-complexes **6** in the diastereoselective iodine–lithium exchange on 1,1-diiodoalkanes **5**. The results obtained are in line with the assumption that the stereodefining step is the irreversible formation of the ate-complexes **6**. As in any mechanistic study, our experiments can only be in line with, but cannot prove such a conjecture.

Experimental

All temperatures quoted are not corrected. ^1H, ^{13}C NMR: Bruker AC-300, AM-400 and AMX-500. Flash chromatography: Kieselgel 60 (0.040–0.063 mm, Merck, Darmstadt). Analytical gas chromatography: Siemens Sichromat 3 with a 30 m × 0.35 mm column with Durabond 5, 1.0 bar He. pH 7 Buffer-solution: $NaH_2PO_4 \cdot 2H_2O$ (56.2 g) and $Na_2HPO_4 \cdot 2H_2O$ (213 g) in H_2O (1 L).

1. 3-(*tert*-Butyldimethylsilyloxy)-1-deutero-4,4-dimethyl-1-iodohex-5-ene (9-d_1) and 5-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-6,6-dimethyl-2-trideuteromethyl-1,1,1-trideuterooct-7-ene (10-d_6)

Following the procedure given[10] for the preparation of **9** and **10**, a pre-cooled (−110 °C) solution of *n*-butyllithium in hexane (0.43 mL, 1.67 M, 0.72 mmol) and pentane (1 mL) was added at −110 °C to a solution of 3-(*tert*-butyldimethylsilyloxy)-1,1-diiodo-4,4-dimethylhex-5-ene (**8**) (235 mg, 0.48 mmol) and deuteroacetone (70 µL, 1.0 mmol) in Trapp solvent mixture (5 mL). The reaction mixture was stirred at −110 °C for 30 min and then allowed to warm to room temperature and stirred for 1 h. Then aqueous pH 7 buffer solution (5 mL) was added and the reaction mixture was extracted with pentane (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The ratio of the yields of the mono-deuterated compounds **9-d_1** and the epoxides **10-d_6** and the diastereomeric ratio of these two products was determined to be **9-d_1**$^{(a/b)}$/**10-d_6**$^{(syn/anti)}$ = $63^{(68/32)}/37^{(89/11)}$, by ^1H NMR spectroscopy of the crude product. The crude product was then chromatographed on silica gel (20 g) with pentane to pentane/*tert*-butyl methyl ether 20:1 to give 92 mg (0.25 mmol, 52%) of **9-d_1** and 49 mg (0.16 mmol, 34%) of **10-d_6** as colorless oils. **9-d_1**: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 0.97 (s, 6H), 1.88 (ddd, J = 14.6, 8.2, 7.3 Hz, 1H), 2.06 (ddd, J = 14.5, 8.2, 2.9 Hz, 1H), 3.09 (dd, J = 8.2, 8.2 Hz), 3.28 (dd, 8.8, 5.1 Hz), together 1H, 3.38 (dd, J = 7.2, 3.1 Hz, 1H), 4.97 (dd, J = 17.8, 1.4 Hz, 1H), 4.97 (dd, J = 10.5, 1.4 Hz, 1H), 5.86 (dd, J = 17.9, 10.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −3.9, −3.4, 4.7 (t, J = 23 Hz), 18.4, 22.8, 24.7, 26.1, 38.2, 42.1, 79.7, 112.0, 145.6. $C_{14}H_{28}DOSiI$ (369.4): calcd. C 45.52, H + D 7.91; found C 45.43, H + D 7.83%. **10-d_6-*syn***: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 0.99 (s, 6H), 1.64–1.72 (m, 2H), 2.85 (dd, J = 6.0, 6.0 Hz, 1H), 3.51 (dd, J = 5.3, 5.3 Hz, 1H), 4.97 (dd, J = 10.5, 1.5 Hz, 1H), 4.97 (dd, J = 17.8, 1.5 Hz, 1H), 5.85 (dd, J = 17.9, 10.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.1, −3.9, 18.2, 22.1, 24.6, 26.0, 33.7, 42.4, 58.3, 62.2, 77.6, 122.0, 145.7. **10-d_6-*anti***: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 3.59 (dd, J = 6.9, 4.1 Hz, 1H), remaining signals hidden. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 26.1, 32.7, 61.9, 111.7, remaining signals hidden. $C_{17}H_{28}D_6O_2Si$ (304.6): calcd. C 67.04, H + D 11.25; found C 66.95, H + D 11.41%.

2. 1,1-Diiodo-4,4-dimethyl-3-(trimethylsilyloxy)pentane (15)

A stream of ozone was introduced at −78 °C into a solution of 5,5-dimethyl-4-(trimethlysilyloxy)hex-1-ene **14** (12.0 g, 60 mmol) in dry CH_2Cl_2 (120 mL) until the blue color persisted. The excess of ozone was removed by a stream of oxygen. Triphenylphosphine (17.3 g, 66 mmol) was then added. After the mixture had reached room temperature the solution was adsorbed onto silica gel (30 g) and chromatographed on silica gel (100 g) with pentane to give a clear liquid. This liquid was immediately dissolved in methanol (30 mL) and hydrazine hydrate (30 mL, 85%) was added, whilst maintaining the reaction at room temperature. After stirring for 1 h the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were dried with Na_2SO_4 and concentrated. The residual oil was immediately dissolved in diethyl ether (100 mL) and triethylamine (50 mL) was added. Iodine was added with stirring until a brown color persisted (*care: evolution of nitrogen*). After 1 h aqueous sodium thiosulfate (50 mL, 20%) was added and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried with Na_2SO_4 and concentrated. The residual liquid was chromatographed on silica gel (100 g) with pentane to give 13.7 g (52%) of **15** as a clear liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.17 (s, 9H), 0.86 (s, 9H), 2.46 (ddd, J = 14.5, 8.9, 3.6 Hz, 1H), 2.50 (ddd, J = 14.5, 10.9, 2.4 Hz, 1H), 3.21 (dd, J = 8.9, 2.4 Hz, 1H), 4.96 (dd, J = 10.9, 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −27.0, 1.1, 26.4, 34.9, 52.0, 81.9. $C_{10}H_{22}OSiI_2$ (440.2): calcd. C 27.28, H 5.04; found C 27.32, H 5.01%.

3. 1,1-Diiodo-4,4-dimethylpentan-3-ol (16)

To a solution of **15** (13.7 g, 31 mmol) in acetonitrile (10 mL) was added HF in acetonitrile (20 mL, 5%). After stirring for 1 h the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with Na_2SO_4 and concentrated. The residual liquid was chromatographed on silica gel (100 g) with pentane–diethyl ether 5:1 to give 11.1 g (97%) of **16** as a colorless solid (mp 55 °C). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (s, 9H), 1.79 (br s, 1H), 2.32 (ddd, $J = 14.7, 9.8, 3.1$ Hz, 1H), 2.47 (ddd, $J = 14.7, 11.5, 2.1$ Hz, 1H), 3.19 (dd, $J = 9.8, 2.1$ Hz, 1H), 5.19 (dd, $J = 11.5, 3.1$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -27.3$, 25.7, 34.4, 50.4, 80.3. $C_7H_{14}OI_2$ (368.0): calcd. C 22.85, H 3.83; found C 22.96, H 4.00%.

4. 3-(*tert*-Butyldimethylsilyloxy)-1,1-diiodo-4,4-dimethylpentane (17)

To a solution of **16** (626 mg, 1.7 mmol) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (0.50 mL, 4.3 mmol) and *tert*-butyldimethylsilyltriflate (0.55 mL, 2.4 mmol). After stirring for 2 h methanol (2 mL) was added and the reaction mixture stirred for a further 1 h. Then aqueous pH 7 buffer solution (5 mL) was added and the reaction mixture was extracted with pentane (5 mL). The combined organic phases were washed with brine (5 mL), dried with Na_2SO_4 and concentrated. The residual liquid was chromatographed on silica gel (30 g) with pentane to give 762 mg (93%) of **17** as a white solid (mp 29 °C). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.10$ (s, 3H), 0.16 (s, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 2.52 (ddd, $J = 14.9, 8.0, 3.4$ Hz, 1H), 2.64 (ddd, $J = 14.9, 11.3, 1.8$ Hz, 1H), 3.13 (dd, $J = 8.0, 1.8$ Hz, 1H), 5.02 (dd, $J = 11.3, 3.4$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -26.9$, −3.8, −3.2, 18.6, 26.2, 26.4, 35.2, 53.4, 81.4. $C_{13}H_{28}OSiI_2$ (482.3): calcd. C 32.37, H 5.85; found C 32.35, H 6.02%.

5. 3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-1-iodopentane (19)

A pre-cooled (–110 °C) solution of *n*-butyllithium in hexane (0.50 mL, 1.42 M, 0.71 mmol) and pentane (1 mL) was added at −110 °C to a solution of **17** (200 mg, 0.42 mmol) in Trapp solvent mixture (4 mL). After 5 min the reaction was quenched with methanol (0.25 mL). Then brine (5 mL) was added and the reaction mixture was extracted with pentane (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated. The residual liquid was chromatographed on silica gel (10 g) with pentane to give 142 mg (96%) of **19** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.08$ (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 0.91 (s, 9H), 1.91 (dddd, $J = 14.5, 8.2, 7.6, 4.8$ Hz, 1H), 2.12 (dddd, $J = 14.8, 8.3, 8.3, 2.7$ Hz, 1H), 3.14 (ddd, $J = 9.3, 8.3, 8.2$ Hz, 1H), 3.29 (dd, $J = 7.5, 2.7$ Hz, 1H), 3.34 (ddd, $J = 9.1, 9.1, 4.8$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -3.9$, −3.3, 18.4, 26.1, 26.4, 35.7, 37.9, 80.6. $C_{13}H_{29}OSiI$ (356.4): calcd. C 43.81, H 8.20; found C 43.98, H 8.44%.

6. Typical procedures for iodine–lithium exchange reactions with compound 17

Quench with deuterated methanol or deuterated thiophenol. 3-(*tert*-Butyldimethylsilyloxy)-1-deutero-4,4-dimethyl-1-iodopentane (**20**): A pre-cooled (−110 °C) solution of *n*-butyllithium in hexane (0.27 mL, 1.50 M, 0.41 mmol) and pentane (1 mL) was added at −110 °C to a solution of **17** (130 mg, 0.27 mmol) in Trapp solvent mixture (2 mL). After the indicated reaction time the reaction was quenched with deuterated methanol (22 µL, 2 equiv.) or deuterated thiophenol (57 µL, 2 equiv.). Then brine (5 mL) was added and the reaction mixture was extracted with pentane (5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated. The residual liquid was chromatographed on silica gel (10 g) with pentane to give **20** as a colorless oil. The ratio of isotopomers was determined by ^2H NMR spectroscopy. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.06$ (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 0.89 (s, 9H), 1.88 (ddd, $J = 14.8, 7.8, 7.5$ Hz, 1H), 2.08 (ddd, $J = 14.4, 8.4, 2.3$ Hz, 1H), 3.10 (dd, $J = 8.3, 8.3$ Hz), 3.31 (dd, $J = 8.8, 4.9$ Hz), together = 1H, 3.27 (dd, $J = 7.6, 2.7$ Hz, 1H). ^2H NMR (400 MHz, $CHCl_3$): $\delta = 3.10$ (br s), 3.31 (br s), together = 1D. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -3.9$, −3.3, 18.5, 26.2, 26.5, 35.7, 37.8, 80.6. $C_{13}H_{28}DOSiI$ (357.4): calcd. C 43.69, H + D 8.18; found C 43.79, H + D 8.27%.

Quench with deuterated acetone. 3-(*tert*-Butyldimethylsilyloxy)-1-deutero-4,4-dimethyl-1-iodopentane (**20**) and 5-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-6,6-dimethyl-2-trideuteromethyl-1,1,1,-trideuteroheptane (**22**): A pre-cooled (−110 °C) solution of *n*-butyllithium in hexane (0.50 mL, 1.43 M, 0.72 mmol) and pentane (1 mL) was added at −110 °C to a solution of **17** (230 mg, 0.48 mmol) in Trapp solvent mixture (5 mL). After the indicated reaction time deuterated acetone (70 µL, 1.0 mmol) was added. The reaction mixture was stirred at −110 °C for 30 min and then allowed to warm to room temperature and stirred for 1 h. Then aqueous pH 7 buffer solution (5 mL) was added and the reaction mixture was extracted with pentane (10 mL). The combined organic phases were washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The ratio of the yields of **20** and **22** as well as the diastereomeric ratio of **22** was determined by ^1H NMR spectroscopy of the crude product. The crude product was then chromatographed on silica gel (20 g) with pentane to pentane–*tert*-butyl methyl ether 10:1 to give **20** and **22** as colorless oils. The ratio of isotopomers of **20** was determined by ^2H NMR spectroscopy. **22-*syn***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.87 (s, 9H), 0.89 (s, 9H), 1.59–1.73 (m, 2H), 2.91 (dd, $J = 5.9, 5.9$ Hz, 1H), 3.44 (dd, $J = 5.2, 5.2$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.1$, −3.8, 18.3, 26.2, 26.4, 33.4, 35.9, 55.8, 62.1, 78.4. **22-*anti***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.04$ (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.90 (s, 9H), 1.55–1.64 (m, 2H), 2.90 (dd, $J = 5.8, 5.8$ Hz, 1H), 3.51 (dd, $J = 7.1, 3.9$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.0$, −3.7, 18.4, 26.1, 26.6, 32.3, 35.8, 55.8, 62.1, 78.1.

7. Typical procedure for iodine–lithium exchange on compound 2

1-Iodo-2-phenylethane and 1-deutero-1-iodo-2-phenylethane: A pre-cooled (−110 °C) solution of *n*-butyllithium in hexane (0.48 mL, 1.50 M, 0.72 mmol) and pentane (1 mL) was added at −110 °C to a solution of 1,1-diiodo-2-phenylethane (**2**) (172 mg, 0.48 mmol) in Trapp solvent mixture (5 mL). After the indicated reaction time the reaction was quenched with a 1:1 mixture of methanol and deuterated methanol (0.50 mL, 40 equiv.). Then brine (5 mL) was added and the reaction mixture was extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated. The residual liquid was chromatographed on silica gel (10 g) with pentane to give a mixture of 1-iodo-2-phenylethane and 1-deutero-1-iodo-2-phenylethane as a colorless oil. The ratio of these two products was determined by ^1H NMR spectroscopy. Reaction quenched after 5, 30, 150 min, yield 85, 77, 59%, k_H/k_D 0.5, 0.6, 1.1.

The undeuterated and the monodeuterated 1-iodo-2-phenylethane were synthesized independently for analysis according to the above procedure in 98% yield by quenching with either methanol or deuterated methanol after 10 min. 1-Iodo-2-phenylethane: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.11$ (t, $J = 7.7$ Hz, 2H), 3.28 (t, $J = 7.7$ Hz, 2H), 7.11–7.27 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 5.3$, 40.3, 126.8, 128.3, 128.6, 140.6. C_8H_9I (232.1): calcd. C 41.41, H 3.91; found C 41.33, H 3.84%. 1-Deutero-1-iodo-2-phenylethane: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.10$ (d, $J = 7.7$ Hz, 2H), 3.27 (tt, $J_{HH} = 7.7$ Hz, $J_{HD} = 1.1$ Hz, 1H), 7.11–7.27 (m, 5H). ^{13}C NMR (75 MHz,

$CDCl_3$): $\delta = 5.3$ (t, $J_{CD} = 22.7$ Hz), 40.3, 126.8, 128.3, 128.6, 140.6. C_8H_8DI (233.1): calcd. C 41.23, H + D 3.89; found C 41.52, H + D 4.19%.

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